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ii. Animal Studies

- (a) Tobacco extract but not nicotine impairs the mechanical strength of fracture healing in rats.
- (b) Potentially Reduced Exposure Cigarettes Accelerate Atherosclerosis: Evidence for the Role of Nicotine

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i. Evaluation of the Abuse Liability of Very Low Nicotine Cigarettes (NCT0359751)

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- ii. Evaluation of the Abuse Liability of Very Low Nicotine Mentholated Cigarettes (NCT03559725)
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- iii. A Longitudinal Ambulatory Study to Assess Changes in Cigarettes Consumption Behavior and Biomarkers of Exposure during a 6-Week switch to Very Low Nicotine (NCT03571724)
 - (a) Study Design
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- iv. A prospective, double-blind, randomized, active controlled, parallel group, multicenter phase II clinical trial to evaluate the effectiveness of X-22 as a smoking cessation aid (NCT01400815).
- v. A randomized trial of nicotine replacement therapy in combination with reduced-nicotine cigarettes for smoking cessation (IND 69,185).
- vi. Reduced nicotine content cigarettes: effects on toxicant exposure, dependence and cessation (NCT00777569).
- vii. Randomized trial of reduced-nicotine standards for cigarettes (NCT01681875).
- viii. Transient compensatory smoking in response to placebo cigarettes.
- ix. A Randomized Controlled Trial of Progressively Reduced Nicotine Content Cigarettes on Smoking Behaviors, Biomarkers of Exposure, and Subjective Ratings.
- x. New lower nicotine cigarettes can produce compensatory smoking and increased carbon monoxide exposure.
- xi. The acute effects of nicotine on the subjective and behavioural responses to denicotinized tobacco in dependent smokers
- xii. The effects of nicotine, denicotinized tobacco, and nicotine-containing tobacco on cigarette craving, withdrawal, and self-administration in male and female smokers.
- xiii. Smoking Topography Characteristics of Very Low Nicotine Content Cigarettes, With and Without Nicotine Replacement, in Smokers with Schizophrenia and Controls.
- xiv. The impact of smoking very low nicotine content cigarettes on alcohol use.
- xv. Nondaily smokers' changes in cigarette consumption with very low-nicotine-content cigarettes. A randomized double-blind clinical trial (NCT02228824).
- xvi. Response to varying the nicotine content of cigarettes in vulnerable populations: An initial experimental examination of acute effects.
- xvii. Nicotine and Anatabine Exposure from Very Low Nicotine Content Cigarettes.
- xviii. Alcohol-induced increases in smoking behavior for nicotinized and denicotinized cigarettes in men and women.

- xix. Greater reductions in nicotine exposure while smoking very low nicotine content cigarettes predict smoking cessation.
- xx. Reduced nicotine content cigarettes and use of alternative nicotine products: Exploratory trial.
- xxi. Abrupt nicotine reduction as an endgame policy: A randomized trial.
- xxii. Evaluation of a reduced nicotine product standard: Moderating effects of and impact on cannabis use.
- xxiii. Treating smokers before the quit date: Can nicotine patches and denicotinized cigarettes reduce cravings?
- xxiv. Effects of 6-week use of reduced-nicotine content cigarettes in smokers with and without elevated depressive symptoms.
- xxv. A prospective, double-blind, randomized, active controlled, parallel group, multicenter phase II clinical trial to evaluate the effectiveness of Quest alone and in combination with nicotine replacement therapy as a smoking cessation aid (IND 69,185).
- xxvi. Sex differences in acute relief of abstinence-induced withdrawal and negative affect due to nicotine content in cigarettes.
- xxvii. Reduced Nicotine Content Cigarettes and Nicotine Patch.
- xxviii. Reduced nicotine cigarettes: Smoking behavior and biomarkers of exposure in smokers not intending to quit.
- xxix. Prolonged exposure to denicotinized cigarettes with or without transdermal nicotine.
- xxx. The combined effect of very low nicotine content cigarettes, used as an adjunct to usual Quitline care (nicotine replacement therapy and behavioural support), on smoking cessation: a randomized controlled trial (ACTRN126080004103580).
- xxxi. Reduced-nicotine cigarettes in young smokers: Impact of nicotine metabolism on nicotine dose effects.
- xxxii. Pharmacodynamic effects of new de-nicotinized cigarettes.
- xxxiii. Smoking topography in response to denicotinized and high-yield nicotine cigarettes in adolescent smokers.
- xxxiv. Sex differences in response to reduced nicotine content cigarettes.
- xxxv. Complementing the standard multicomponent treatment for smokers with denicotinized cigarettes: A randomized trial.
- xxxvi. Cognitive effects of very low nicotine content cigarettes, with and without nicotine replacement, in smokers with schizophrenia and controls.
- xxxvii. Mouth-level intake of benzo[a]pyrene from reduced nicotine cigarettes.
- xxxviii. Dose-Response Effects of Spectrum Research Cigarettes.

- xxxix. Effects of reduced nicotine content cigarettes on individual withdrawal symptoms over time and during abstinence (NCT01681875).
- xl. Nicotine and non-nicotine smoking factors differentially modulate craving, withdrawal and cerebral blood flow as measured by arterial spin labeling.
- xli. Experimental evidence for a causal relationship between smoking lapse and relapse.
- xlii. Decreasing nicotine content reduces subjective and physiological effects of smoking.
- xliii. Evaluating the acute effects of oral, non-combustible potential reduced exposure products marketed to smokers.
- xliv. The airway sensory impact of nicotine contributes to the conditioned reinforcing effects of individual puffs from cigarettes.
- xlv. Placebo cigarettes in a spaced smoking paradigm.
- xlvi. Reducing nicotine exposure results in weight gain in smokers randomized to very low nicotine content cigarettes.
- xlvii. Separate and combined effects of very low nicotine cigarettes and nicotine replacement in smokers with schizophrenia and controls.
- xlviii. Adolescent smokers' response to reducing the nicotine content of cigarettes: Acute effects on withdrawal symptoms and subjective evaluations.
- xlix. Smoking in the absence of nicotine: behavioral, subjective and physiological effects over 11 days.
 - I. Estimations and predictors of non-compliance in switchers to reduced nicotine content cigarettes.
 - li. Preliminary test of cigarette nicotine discrimination threshold in non-dependent versus dependent smokers.
 - lii. Effects of low nicotine content cigarettes on smoke intake.
 - liii. Age moderates smokers' subjective response to very-low nicotine content cigarettes: Evidence from a randomized controlled trial.
 - liv. Sex differences in tobacco withdrawal and responses to smoking reduced-nicotine cigarettes in young smokers.
 - lv. Response to reduced nicotine content cigarette among smokers differing in tobacco dependence severity.
 - lvi. Cigarette nicotine content as a moderator of the relationship between negative effect and smoking (NCT01681875).
 - lvii. Effects of acute abstinence and nicotine administration on taste perception in cigarette smokers.
 - lviii. Threshold dose for discrimination of nicotine via cigarette smoking.
 - lix. Estimation of compliance with exclusive smoking of very low nicotine content cigarettes using plasma cotinine.

- ix. Addiction potential of cigarettes with reduced nicotine content in populations with psychiatric disorders and other vulnerabilities to tobacco addiction.
- xi. The influence of nicotine dose and nicotine dose expectancy on the cognitive and subjective effects of cigarette smoking.
- lxii. Effect of Immediate vs Gradual Reduction in Nicotine Content of Cigarettes on Biomarkers of Smoke Exposure: A Randomized Clinical Trial.
- lxiii. Preliminary Validity of the Modified Cigarette Evaluation Questionnaire in predicting the reinforcing effects of cigarettes that vary in nicotine content.
- lxiv. Reduced-nicotine cigarettes increase platelet activation in smokers in vivo: A dilemma in harm reduction.
- lxv. Pharmacokinetic Profile of Spectrum Reduced Nicotine Cigarettes.
- lxvi. Response to reduced Nicotine Content in Vulnerable Populations: Effect of Menthol Status (NCT02250534).
- lxvii. Evaluation of menthol per se on acute perceptions and behavioral choice of cigarettes differing in nicotine content.
- lxviii. The Impact of Nicotine Dose on the Reinforcing Value of Cigarettes in Adolescents.

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- iv. Effects of Nicotine Reduction on Smoking Behavior in ADHD Smokers
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- vi. Manipulating Tobacco Constituents in Female Menthol Smokers
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- viii. Project 1, Study 2: Extended Exposure to Low Nicotine Content Cigarettes in Childbearing Age Women
- ix. Project 1, Study 2: The Combined Impact of Nicotine Replacement and Spectrum Cigarettes
- x. Project 2, Study 2: Extended Exposure to Low Nicotine Content Cigarettes in Opioid Abusers
- xi. Project 3, Study 2: Extended Exposure to Low Nicotine Content Cigarettes in People With Current Affective Disorders
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- xviii. Very Low-Nicotine Cigarettes in Smokers With SUD

- xix. Neuroimaging Reward, Behavioral Treatment, and Smoking Cessation
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- xxii. Reactions to Reduced Nicotine Cigarettes in Young Adult Low-Frequency Smokers (NicRed)
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2. Quantitative Study to Develop VLN™ Hypothetical Product Messages Among U.S. Adult Cigarette Smokers, Adult Former Cigarette Smokers and Adult Never Cigarette Users

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